Conferences and Reviews

Familial Benign Hypercalcemia—From Clinical Description to Molecular Genetics

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Familial benign hypercalcemia (or familial hypocalciuric hypercalcemia), a syndrome of lifelong hypercalcemia inherited as an autosomal dominant trait, is distinct from the multiple endocrine neoplasia syndromes and other forms of inherited parathyroid disease. Familial benign hypercalcemia results from the inappropriate secretion of parathyroid hormone despite hypercalcemia, enhanced renal tubular reabsorption of calcium (independent of parathyroid hormone), and apparent tissue resistance to adverse effects of hypercalcemia. Heterozygosity for the familial hypercalcemia trait is benign, although homozygosity for the trait may lead to severe neonatal primary hyperparathyroidism. Genetic linkage studies show that most persons affected with familial hypercalcemia have a mutation on the long arm of chromosome 3 (3cen–q21), although one phenotypically indistinguishable family appears to have a mutation on the short arm of chromosome 19 (19p), and another family has neither 3q nor 19p mutations. One group has recently shown mutations in a putative parathyroid cell-surface calcium receptor that are plausible causes for the chromosome 3q variant of the familial hypercalcemia syndrome. Perhaps the other genes for this syndrome encode proteins representing hitherto-unknown regulators of systemic calcium metabolism independent of parathyroid cell calcium sensing or proteins involved in signal transduction from the calcium receptor.

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In this article I give a brief overview of familial benign hypercalcemia (FBH),[1-4] which has also been reported as familial hypocalciuric hypercalcemia and hereditary hyperparathyroidism.[5,6] After a historical introduction, I summarize the abnormalities of the syndrome, review new data that establish the existence of at least three genetically distinct but phenotypically indistinguishable forms,[7] and outline recent evidence for specific mutations causing one form of FBH. This is not a comprehensive review; only selected articles are cited, and for some issues, detailed reviews cited will give access to the original citations.

Historical Background

The first family recognizable in the literature as having the familial benign hypercalcemia syndrome was a kindred reported in 1966 among seven families thought to have hereditary primary hyperparathyroidism.[5,8] This family had symptomless hypercalcemia without clear evidence of parathyroid hormone (PTH) hypersecretion.[8] Subtotal parathyroidectomy was unsuccessful in relieving the hypercalcemia, and it was suggested that the condition may be a new one.[8] In 1972 a second family with this syndrome was described, and the syndrome was named "familial benign hypercalcemia."[1] The essential features of the FBH syndrome were defined in that report, including hypercalcemia, mild hypophosphatemia, normal serum alkaline phosphatase levels, normal serum levels of immunoreactive parathyroid hormone, mild hypermagnesemia, the absence of hypercalciuria, and the failure of subtotal parathyroidectomy to return serum calcium levels to normal. In 1977 several families with the FBH syndrome were reported, and in recognition of the relatively low urinary calcium excretion, the term "familial hypocalciuric hypercalcemia" was devised.[6]

Since these initial descriptions, more than 50 families and over 250 affected persons have been described as having the FBH syndrome, and the clinical characteristics have been extensively validated.[1-4,9-12]

Clinical Characteristics

The features of FBH are compared and contrasted with those of sporadic and familial primary hyperparathyroidism in Table 1. Clinically, FBH is a bland syndrome that is almost always found serendipitously by serum calcium measurement. Although there is some disagreement,[2] our studies and those of others[3,4,10,11] suggest that what might appear to be symptoms of FBH result from

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ABBREVIATIONS USED IN TEXT

FBH = familial benign hypercalcemia
PCR = polymerase chain reaction
PTH = parathyroid hormone

ascertainment bias: probands seek medical care for some reason, and hypercalcemia is detected incidentally. Persons ascertained by screening have no more symptoms than their unaffected relatives.[3] A few reports suggest that FBH may cause recurrent acute pancreatitis, but this, too, may represent ascertainment bias artifact because physicians routinely test for hypercalcemia in patients with pancreatitis.[13] As described later, severe primary hyperparathyroidism of neonates may be an uncommon manifestation of FBH. Unlike patients with typical primary hyperparathyroidism, those affected with FBH do not have osteopenia,[14,15] hyposthenuria,[16] or other symptoms of hypercalcemia.[1,3,4,10,11] Nonetheless, having FBH can be a substantial health problem because it can masquerade as primary hyperparathyroidism so closely that it is totally indistinguishable with available tests.[4]

Renal Function in Familial Benign Hypercalcemia

The renal difficulties seen in patients with severe primary hyperparathyroidism are virtually absent in FBH. The glomerular filtration rate is well maintained into advanced age,[3] and maximal urinary concentrating ability is preserved in FBH versus the hyposthenuria that accompanies primary hyperparathyroidism.[16] Urinary excretion of cyclic adenosine monophosphate is generally normal in FBH, suggesting no excess action of PTH on the kidneys.[3,10]

The urinary excretion of calcium is virtually never elevated in patients with FBH. In our detailed studies of 21 families, 75% of affected family members excreted less than 2.5 mmol of calcium per day (100 mg per 24 hours) (average, 2.2 mmol per day).[3] Urinary calcium excretion may reach 6.2 mmol per day (250 mg per 24 hours), however.[2,3] One patient my group studied excreted 5.0 to 6.2 mmol of calcium per day (200 to 250 mg per 24 hours) and has had several episodes of calcium oxalate urolithiasis (unpublished results). Perhaps he has both FBH and idiopathic hypercalciuria. As noted earlier, even in the absence of PTH, there is enhanced renal tubular reabsorption of calcium (and magnesium) in patients with FBH, in comparison with persons inadvertently made hypoparathyroid after the removal of sporadic parathyroid adenomas.[4] Studies with diuretics and lithium suggest that the site of enhanced renal tubular calcium reabsorption is either the proximal nephron or the ascending limb of the loop of Henle.[4]

Abnormal Function of Parathyroid Glands

The hypercalcemia of FBH is not due to abnormal protein binding, as serum protein concentrations are normal and serum ionized calcium levels are elevated. Only a few persons have clinically overt hypophosphatemia, although in some it can be noteworthy. On average, the serum magnesium concentration in affected persons is at about the upper limit of normal. Generally, serum alkaline phosphatase activity is normal in FBH. Thus, the only biochemical sign of PTH excess in most patients is hypercalcemia.[1-4,9-12]

Initial data about serum immunoreactive PTH levels in FBH were widely discrepant (reviewed by Law and coworkers).[17] The exact reasons for the discrepancies are not

TABLE 1.—*Clinical and Biochemical Features of Sporadic and Familial Hyperparathyroidism (Primary HPT) Versus Familial Benign Hypercalcemia*

Variable	*Sporadic Primary HPT*	*Familial Primary HPT*	*Familial Benign Hypercalcemia*
Age of onset	Generally >40 years	Variable*	Birth
Serum or plasma level			
Calcium	Elevated	Elevated	Elevated
Magnesium	Variable	Variable	Normal to elevated
Inorganic phosphorus	Normal to very low†	Normal to very low†	Normal to mildly decreased
Calcitriol‡	Normal to elevated†	Normal to elevated†	Normal to slightly decreased
Intact parathyroid hormone	Increased§	Increased§	Normal‖
Urinary excretion			
Cyclic AMP	High normal to increased¶	High normal to increased¶	Normal to mildly increased
24-Hr calcium excretion	Variable#	Low to elevated	Normal to low**
Calcium clearance:creatinine clearance ratio	Usually >0.02††	Usually >0.02	Generally <0.01‡‡
Other findings	Occasional signs of hyperparathyroid bone disease, chondrocalcinosis, urolithiasis; enlarged parathyroid gland by ultrasonography	Occasional signs of hyperparathyroid bone disease, chondrocalcinosis, urolithiasis; enlarged parathyroid gland(s) by ultrasonography	Occasional chondrocalcinosis, possible gallstones

cyclic AMP = cyclic adenosine monophosphate

*The condition can appear as early as childhood to as late as midlife.
†Present in 50% of persons tested.
‡Calcitriol = 1,25-dihydroxyvitamin D.
§Hormone levels are increased in 80% to 90% of persons tested.
‖Intact parathyroid hormone levels are increased in 15% of persons tested.
¶Occurring in more than 75% of persons tested.
#Urinary calcium excretion is increased in 30% to 50% of persons tested.
**Excretion is <100 mg/day in 75% of persons tested.
††Occasionally the ratio is <0.01.
‡‡The ratio is almost never >0.02.

known, but the development of two-site immunometric assays for PTH has clarified things considerably. We measured PTH levels in the serum of FBH subjects by midregion radioimmunoassay, bioassay, and two different two-site immunometric assays, with remarkably similar findings.[18,19] Serum intact and bioactive PTH levels cluster in the lower half of the normal range for most persons having FBH, but some are in the upper half of the normal range, and 10% to 20% are mildly elevated. In contrast, serum PTH concentrations are unmistakably elevated in 80% to 90% of patients who have primary hyperparathyroidism.[18,19] The diagnostic approach to this difficult problem (elevated PTH levels in FBH) has been discussed elsewhere.[4]

The "normal" concentrations of serum PTH in most hypercalcemic patients with FBH are paradoxical and suggest a priori an abnormality of parathyroid gland function. Indeed, parathyroidectomy causes hypocalcemia in patients with FBH, establishing that the hypercalcemia is PTH-dependent. The relationship between the degree of calcemia and the level of serum PTH, however, differs from that in primary hyperparathyroidism (Figures 1 and 2). A positive linear relationship has been shown between serum calcium and serum intact PTH levels in persons with FBH, which had been known for a long time to be the case in primary hyperparathyroidism.[19] The relationships are different between the two diseases, however, both for serum calcium (Figure 1) and inorganic phosphorus (Figure 2). Primary hyperparathyroidism appears to be characterized by subnormal sensitivity to PTH, as would be expected from receptor internalization or desensitization in response to hormone excess. Relatively speaking, then, people with FBH are more sensitive to PTH than those with primary hyperparathyroidism. Tissue sensitivity to PTH is probably not actually increased in FBH.[4,19] Remarkably, serum levels of PTH are low in some patients with FBH,[18,19] consistent with the thought that excess PTH is not the sole cause of the hypercalcemia.

Alterations in the set point for the calcium suppression of PTH secretion have been described for cells derived from parathyroid adenomas.[20,21] We examined PTH suppressibility in normal volunteers, patients with FBH, and those with primary hyperparathyroidism (Figure 3).[22] Calcium infusion that raised serum calcium levels identically in the three groups fully suppressed PTH levels in those with FBH, but suppression was incomplete in patients with primary hyperparathyroidism. Log transformation of the data (Figure 4) demonstrates more clearly the rightward shift of the calcium:PTH secretion dose-response curve in FBH, but with no change in slope or in final achieved PTH levels. In contrast, patients with hyperparathyroidism had both a rightward shift of the dose-response curve and variable degrees of PTH nonsuppressibility that were related to tumor mass.[22]

Neonates in FBH families rarely may have unusual parathyroid abnormalities. Severe neonatal hyperparathyroidism with diffuse parathyroid hyperplasia has been reported to occur in children with one or both parents affected[23]; it is not clear if homozygosity for the FBH trait is always required for neonatal hyperparathyroidism to occur. This is in contrast to normal or mildly hyperplastic parathyroid tissue found in adults with FBH.[2,3] Many af-

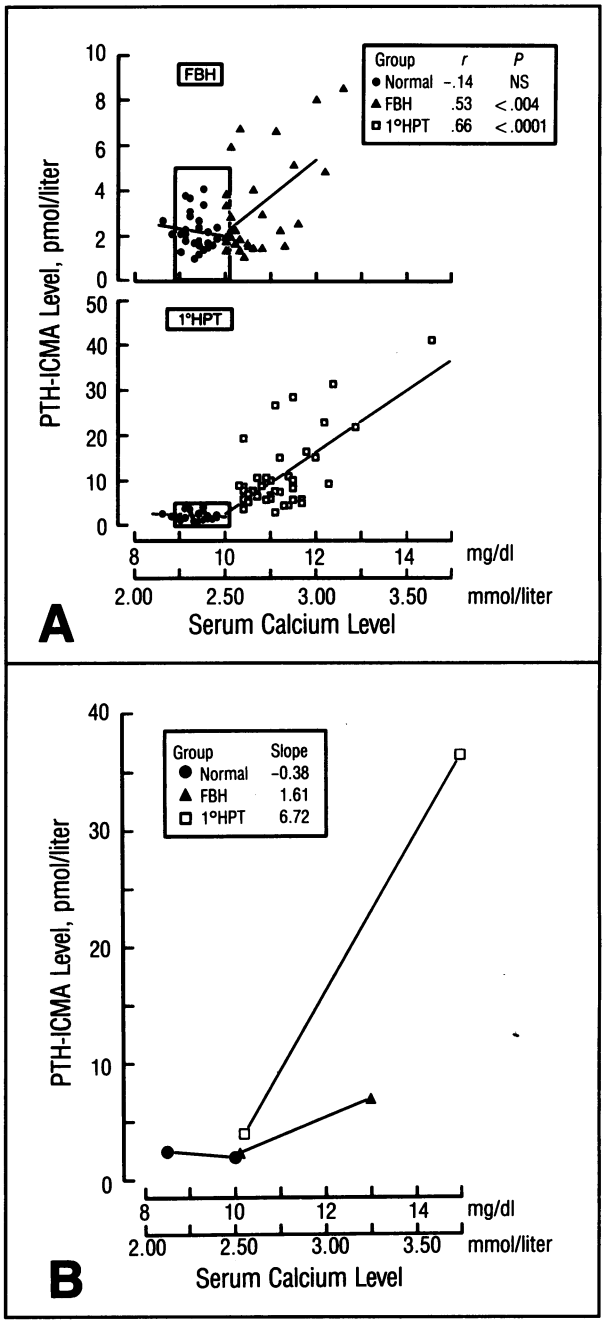

Figure 1.—Plasma intact parathyroid hormone levels by immunochemiluminometric assay (PTH-ICMA) as a function of serum calcium levels are shown in normal controls, patients with familial benign hypercalcemia (FBH), and patients with primary hyperparathyroidism (1°HPT). **A,** The upper panel shows data for normal controls contrasted with data for those with FBH; the lower panel contrasts data from patients with 1°HPT with data from normal controls (note different vertical scales). **B,** Regression lines for all three data sets are shown on the same scale. The boxes in panel A represent limits of normal values (from Firek et al[19]). NS = not significant

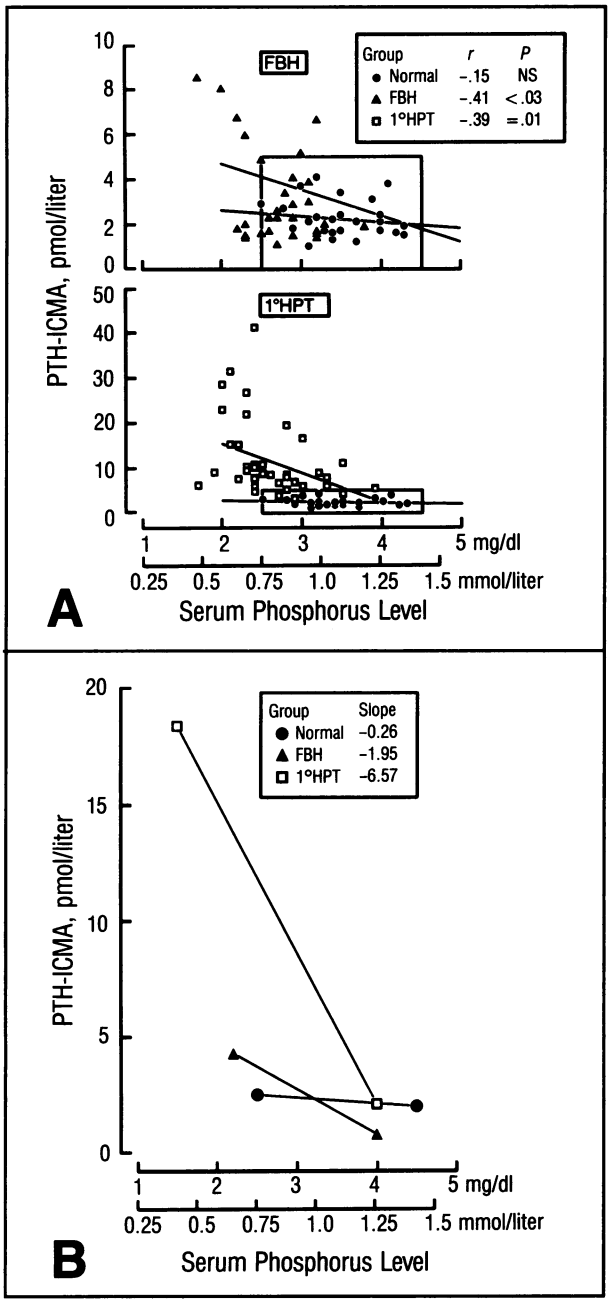

Figure 2.—Plasma intact parathyroid hormone levels by immunochemiluminometric assay (PTH-ICMA) are shown as a function of serum inorganic phosphorus in normal controls and subjects with familial benign hypercalcemia (FBH) and primary hyperparathyroidism (1°HPT). Symbols and overall layout are the same as in Figure 1 (from Firek et al[19]).

fected with neonatal severe primary hyperparathyroidism who also have FBH have been treated with subtotal parathyroidectomy, but the infants may recover with conservative therapy.[24,25] In contrast, unaffected babies of women with FBH may suffer prolonged hypocalcemia.[26]

Unifying Pathophysiologic Hypothesis

From the studies of renal and parathyroid function in FBH, it appears that affected persons have at least two defects, a persistence of normal PTH secretion in the face of hypercalcemia and PTH-independent, enhanced renal tubular reabsorption of calcium. What single genetic mutation could result in these two abnormalities? New evidence, reviewed in the following sections, suggests that an integral plasma membrane protein common to the two organs is involved in calcium sensing, calcium transport, or both, and that one of several mutations in that gene may be related to one form of FBH.*

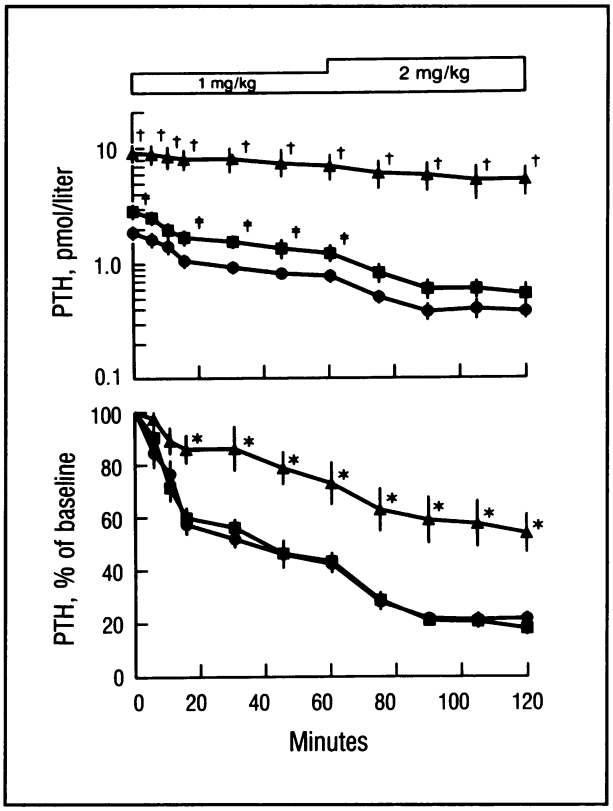

Figure 3.—Changes in plasma intact parathyroid hormone (PTH) levels are shown as a function of time during calcium infusion in normal control subjects (•), patients with familial benign hypercalcemia (FBH, ■), and patients with primary hyperparathyroidism (1°HPT, ▲). The top panel shows the absolute concentration of PTH versus time; in the bottom panel, PTH is expressed as a percentage of the basal or initial concentration. * = $P < .001$, HPT versus normal controls or FBH; † = $P < .005$, HPT versus normal controls or FBH; ‡ = $P < .05$, FBH versus normal controls. The vertical lines represent ±1 standard error of the mean. The calcium infusion rate is depicted at the top of the figure (from Khosla et al[22]).

Epidemiology and Genetics

The incidence and prevalence of FBH are unknown. As reported from the National Institutes of Health, 9% of patients referred after failed neck explorations for suspected primary hyperparathyroidism had FBH.[27] Probably fewer than 30% of all patients with primary hyperparathyroidism undergo surgical therapy,[28] and of those who do, more than 90% are cured after one operation.

*See also the editorial by G. J. Strewler, MD, "Familial Benign Hypocalciuric Hypercalcemia—From the Clinic to the Calcium Sensor," on pages 579-580 of this issue.

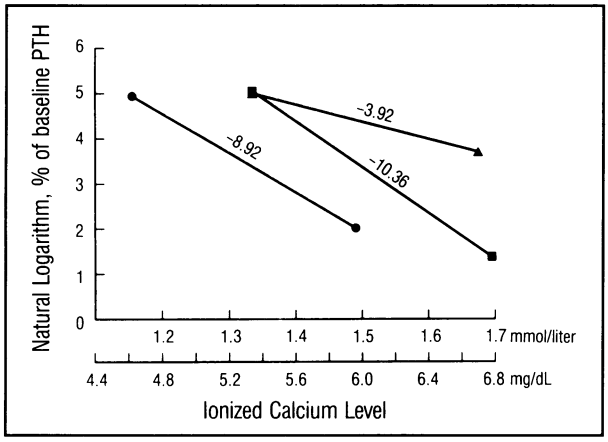

Figure 4.—Relationship is shown between the natural logarithm of the percentage of baseline parathyroid hormone (PTH), and ionized calcium in normal subjects (●) and in patients with familial benign hypercalcemia (FBH, ■), and primary hyperparathyroidism (1°HPT, ▲). Numbers are the slopes of the respective regression lines. The *P* values for comparisons of the slopes are as follows: normal versus FBH, .357; normal versus 1°HPT, .004; FBH versus 1°HPT, .001 (from Khosla et al[22]).

Furthermore, only a minority of patients with hyperparathyroidism are referred to a major center like the National Institutes of Health, resulting in substantial referral bias. For example, major centers are more likely to receive patients who have had more than one failed neck exploration or who have some other unusual problem.[27] Thus, patients with FBH must constitute only a tiny fraction of all patients with hypercalcemia. Because the disorder is essentially asymptomatic, it is seldom detected except incidentally or in family screening, making it difficult to know the actual prevalence. Because the trait is essentially harmless to reproductive capacity and survival, there would appear to be no major adverse selection pressure on patients carrying the FBH gene, and the trait might therefore become increasingly common.

All observers agree that the pattern of FBH in families suggests autosomal dominant inheritance with essentially complete penetrance (example of pedigree in Figure 5). Some clinical observations have suggested that there is a notable excess of affected persons in the kindreds.[2,3,10] This impression was probably created by difficulties with blood sampling and interpretation of serum calcium values in earlier studies. Blood specimens have often been taken under uncontrolled circumstances in local hospital laboratories or private physicians' offices and mailed to the investigating centers. There was no way for the investigators to exclude tourniquet stasis, for example, which falsely elevates serum total calcium values. Furthermore, many of the family groups in which an excess number of affected persons appeared represented infants and juveniles. Hypercalcemia was likely diagnosed in some young patients without the higher normal range for serum calcium levels in children than in adults being taken into account.[29] In recent studies for which affection status (diagnoses) was extensively validated, 46.4% were affected, 47.9% were unaffected, and 5.7% were unclassifiable in families at risk.[7-30] These data suggest that simple autosomal dominant inheritance exists without any effect of the FBH trait on implantation, development, or delivery.

Genetic Linkage Analysis in Familial Benign Hypercalcemia

A few years ago, further pathophysiologic studies in patients or readily accessible tissues[31,32] seemed unlikely to determine quickly the molecular basis of the FBH syndrome. For this reason, several groups began using modern techniques of genetic linkage analysis[33,34] for a "reverse genetics" or "positional cloning" approach to finding the gene mutated in FBH. Underlying genetic linkage analysis is the principle of genetic recombination during meiosis.[35] Modern genetic linkage analysis requires preparing leukocyte DNA from as many members of as many families as possible, firmly establishing the affection status in each person (affected, unaffected, or unknown), and using the DNA to trace inheritance of polymorphic alleles that are known to reside at specific chromosomal locations. Coinheritance of a given polymorphic allele with the disease trait establishes a statistical probability of physical continuity between the marker locus and the mutated gene responsible for the disease.[33-35] Polymorphic alleles can be detected as restriction fragment length polymorphisms, the most highly polymorphic of which are called variable-number tandem repeats. The newest and most powerful tool in the linkage armamentarium, however, is the detection of highly polymorphic dinucleotide, trinucleotide, or tetranucleotide repeat sequences—such as $(CA)_n$, $(AAAG)_n$, and $(AGAT)_n$—by selective amplification of sequence-tagged sites using the polymerase chain reaction (PCR).[36] The sequence-tagged sites are mapped to specific loci[37,38]; PCR primers are constructed to flank the polymorphic sequences, and radioactive products are separated on large polyacrylamide gels for radioautography and scoring. Some PCR-based polymorphisms manifest more than 20 alleles and a high prevalence of heterozygosity, greatly increasing the power of linkage analysis. The use of PCR also decreases by orders of magnitude the amount of DNA needed for linkage studies.

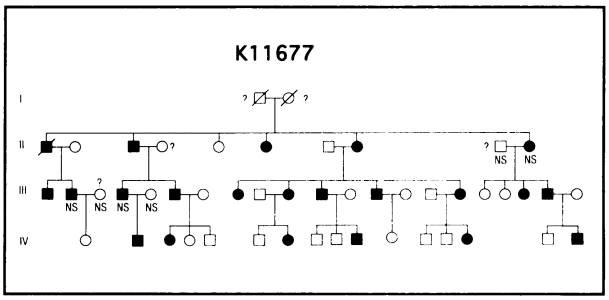

Figure 5.—A pedigree is shown for a representative large family having familial benign hypercalcemia in which the trait was mapped to chromosome 3q (from Heath et al[7]). The squares denote males, the circles females. Filled symbols denote persons affected with the disorder, and a diagonal line indicates that the person is deceased. NS = not sampled, ? = affection status unknown

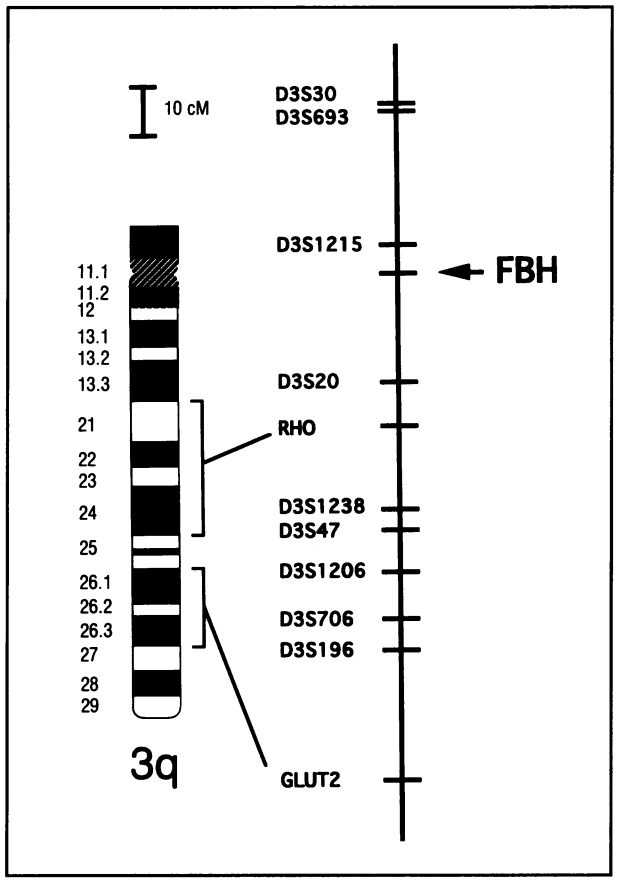

Figure 6.—The schematic diagram shows chromosome 3, with the genetic map showing the relative location of markers linked to the phenotype for familial benign hypercalcemia (FBH_{3q}) in 4 families and the calculated placement of the FBH locus (**arrow**). Note that the bulk of the short arm is omitted from the diagram. Distances between the markers are in centimorgans (cMs; recombination units). The numbers at the left represent band numbers on the chromosomal ideogram, and the numbers at the right signify names of specific marker loci, such as D3S30, RHO (from Heath et al[7]).

With the use of such techniques, several candidate genes were excluded from responsibility for FBH, such as the loci for multiple endocrine neoplasia types 1 and 2, PTH, and PTH-related peptide.[30] Other random loci had been excluded earlier by others (reviewed by Heath and Leppert).[30] More recently, a general linkage search was conducted in which the genome was screened for cosegregation of the FBH trait and numerous polymorphic markers.[39] In four unrelated families, a high probability was established that the gene mutated in FBH families resided on the long arm (q) of chromosome 3 at the position designated 3q21–q24 (bands 21 to 24 of the long arm). In studies of five different families,[7] my group confirmed that the FBH trait cosegregated with markers on chromosome 3q in four. The chromosomal location 3cen–q21—the trait lying somewhere between the centromere (cen) and band 21 on the long arm of chromosome 3 (Figure 6)—was more centromeric than reported previously.[39] To our surprise, we also demonstrated that in a single family, the FBH trait was closely linked with markers on the short arm (p) of chromosome 19.[7] This 19p family was phenotypically indistinguishable from the other families, except that they had milder hypercalcemia than all but one of the 3q families. Since the publication under discussion,[7] we have examined many additional families and have found the FBH trait linked only to chromosome 3q markers (unpublished results). Moreover, linkage of the FBH trait to markers on chromosome 3q has been reported in three more families.[40] In a report in abstract form, a family with FBH was evaluated in whom there was linkage to neither 3q nor 19p markers, suggesting that there are at least three genetically distinct forms of FBH, which I propose to designate as FBH_{3q}, FBH_{19p}, and FBH_0.[41]

Research may have uncovered the first specific mutations causing a form of FBH, the FBH_{3q} variant.[40] The complementary DNA for a putative bovine parathyroid cell-surface calcium receptor, which appears to be a G protein-coupled structure with seven transmembrane-spanning domains, was cloned.[42] Probes for the bovine receptor were used to screen three families thought to have FBH_{3q}, and three distinct mutations were found, two in what is thought to be the extracellular domain of the protein and one in the third intracellular loop.[40] The latter mutation was tested in vitro and affected the calcium-sensing function of the protein. The mutations were reported in three families not reported on previously,[39] so it is unclear if all FBH_{3q} families will have mutations in the same areas of the gene.

These new data are exciting for several reasons:

- It appears that most families showing the FBH phenotype have mutations at the same genetic locus and probably in the same gene.[7,39,40]
- The FBH_{3q} variant appears to result from mutations in a new regulatory protein that will be a fascinating subject for physiologic study.[43]
- Knowledge that there are three distinct mutations causing the FBH phenotype expands the scope of the inquiry considerably and suggests that there may be in addition to mutations in the parathyroid cell-calcium receptor[40] alterations in hitherto-unknown related calcium-sensing or calcium-transport proteins. Alternatively, perhaps the FBH_{19p} and FBH_0 mutations alter signal transduction mechanisms downstream from the parathyroid cell calcium receptor.
- Knowledge that the calcium receptor protein is expressed in renal tissue suggests a unifying explanation for the parathyroid and renal manifestations of FBH.[42]

There is a great need now to obtain specimens from all known FBH families so that their DNA may be incorporated into ongoing linkage and mutational analyses. More families with the FBH_{19p} and FBH_0 variants are needed for refinement of the chromosomal locations and eventual cloning of the mutated genes. Even small families unsuitable for linkage analysis should be sampled to determine the frequency and functional effects of various mutations. That there will be many additional allelic mutations for

FBH_{3q}, resulting in the variable clinical phenotype, seems likely. For example, perhaps only certain mutations can result in the severe neonatal hyperparathyroidism phenotype or in the relatively greater hypercalcemia some families manifest.[44]

The Future

In a little more than 20 years, we have gone from the incidental discovery of the FBH syndrome, through clinical description, to extensive pathophysiologic studies that identified the parathyroid glands and the kidneys as the sites of abnormal calcium metabolism, and now to the beginning of specific molecular explanations for the syndrome. The rapidly evolving technology of genetic linkage analysis, plus some good luck and intuitive pursuit of a candidate gene,[40] led to mutations in one form of FBH and to the approximate location of another gene that when mutated causes the clinical phenotype of FBH. Knowledge of the structures and functions of the FBH genes will provide substantial additional information about normal and deranged regulation of plasma calcium. It seems possible—perhaps even likely—that diseases less "benign" than FBH will be associated with other mutations of these genes.[43] For example, is it possible that mutations of the parathyroid cell calcium receptor could be involved in the pathogenesis of parathyroid neoplasms?

Addendum

Since this manuscript was submitted, a report has appeared supporting the concept that severe neonatal primary hyperparathyroidism in FBH_{3q} results from homozygosity for mutations in the parathyroid cell calcium receptor gene.[45] In addition, we have discovered three unique mutations of the calcium receptor gene (distinct from those reported earlier[40]) that co-segregate with the FBH_{3q} phenotype (H.H.H., S. Odelberg, D. Brown, et al, unpublished data, April 1994). Thus, of the six calcium receptor mutations so far found in FBH_{3q}, all are different.

Acknowledgment

Bill Law, Jr, MD, had major responsibility for creating the original clinical resource. Karen Laakso was study coordinator at a key period in the development of these studies. Mark Leppert, MD, Dora Stauffer, Brith Otterud, Virginia Hill, and Donna Brown provided patient and good-humored assistance with the genetic linkage studies. Finally, the author is deeply grateful for the selfless cooperation of the FBH family members.

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MAJOR GUILT

It is
a mother's job
to feel guilt.
I always did guilt
well.
Now
that my child has Crohn's,
I am
excellent.

ARLYN SERBER©
Sausalito, California

MUSHROOMS

Glory when water,
when warm doe-breath
of April ignites spores
quiet as spots
on the backs of deerticks,
a bursting, a magic,
making fawn prints
out of dust.

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